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10/031,289	05/31/2002	Vega Masignani	PP01639.102; 2300-1639	6882

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Chiron Corporation
Intellectual Property Department R440
PO Box 8097
Emeryville, CA 94662-8097

EXAMINER	
DEVI, SARVAMANGALA J N	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/031,289	MASIGNANI ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,9,10,13,15,17,19,21 and 23-33* is/are pending in the application.

4a) Of the above claim(s) *7, 9, 13,15,17,19,21,23,24 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,10 and 25-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

REQUEST FOR CONTINUED EXAMINATION

1) A request for continued 04/04/06 examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 04/04/06 has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 04/04/06 in response to the Advisory Action mailed 12/21/05.

Status of Claims

3) Claim 1 has been amended via the amendment filed 04/04/06.

Claims 1, 7, 9, 10, 13, 15, 17, 19, 21 and 23-33 are pending.

Claims 1, 10 and 25-32 are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Withdrawn

6) The rejection of claim 1 and those dependent therefrom made in paragraph 15 of the Office Action mailed 10/04/05 and maintained in paragraph 7 of the Advisory Action mailed 12/21/05 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn. A new/modified rejection is set forth below.

7) The rejection of claims 1, 10 and 25-32 therefrom made in paragraph 16 of the Office Action mailed 10/04/05 and maintained in paragraph 8 of the Advisory Action mailed 12/21/05 under 35 U.S.C. § 112, first paragraph, as being non-enabled with regard to the scope, is withdrawn. A new/modified rejection is set forth below.

Response to Applicants' Arguments on Lack of Scope of Enablement

8) Applicants contend that they have amended claim 1 to recite that the immune response will be elicited against '*Neisserial meningitidis* strain B', and therefore the claims are more limited in scope such that the immune response that is elicited is further defined. With regard to the art-demonstrated unpredictability, Applicants present the following arguments. (a) Applicants state that the Office's statement on the predictability or lack thereof cannot mean that one of skill in the art must be able to predict the exact sequence of every protein or polypeptide within the claim scope to be predictable. (b) The standard of enablement for claims to polypeptides cannot be that one of skill in the art must be able to predict a *priori* the sequence of every polypeptide within the claimed function with 100% accuracy. If this were the standard, then a claim to 'a monoclonal antibody that binds to a protein of SEQ ID NO: X' would not be enabled because it is indisputable that no one of skill in the art could predict the sequence of every antibody that could meet the claimed function much less the sequence of even one antibody that bind a given protein. (c) A claim to a monoclonal antibody that binds a specified protein is in the class of claims to a polypeptide that has a particular function, since a monoclonal antibody is a peptide and binding to a protein is the function of the monoclonal antibody. (d) The Federal Circuit in *In re Wands* was asked whether a claim to a method using HBsAg monoclonal antibody was enabled when the application only provided one example of a working monoclonal antibody from the IF8 hybridoma that was deposited and therefore accessible to the public. The trial court held the broad claims to use of HBsAg monoclonal antibodies were not enabled by the single monoclonal antibody disclosed, but the Federal Circuit reversed the trial court's holding. The Federal Circuit held that the broad claim to using HBsAg monoclonal antibodies was enabled even though only one working monoclonal antibody was provided because there was a method that would predictably produce monoclonal antibodies within the scope of the claim, i.e., HBsAg monoclonal antibodies. (e) The Wands factor relating to predictability does not mean that one of skill in the art can predict the exact sequence of every protein (such as a monoclonal antibody) or a polypeptide that is within the scope of a claim. The Wands factor relating to predictability is satisfied when there is a routine protocol that will predictably produce the claimed protein or polypeptide commensurate in scope. (f) The Federal Circuit held that the methods of generating monoclonal antibodies were in fact routine and would

produce the HBsAg monoclonal antibodies needed to make and use the claimed invention. This case is similar to the present claimed invention. (g) The application discloses the one sequence, SEQ ID NO: 1331 much like Wands disclosed one HBsAg monoclonal antibody hybridoma. There are routine procedures for making the claimed polypeptides and screening for the claimed function of 'eliciting an immune response in '*Neisserial meningitidis* strain B'.

With regard to the amount of guidance, Applicants contend that this becomes relevant only if the Office's statement of predictability is accurate. Applicants assert that: (a) The predictability relates to whether there are screening methods that will predictably identify polypeptides with the claimed function. (b) It is well established that guidance relating to routine methods need not be provided if they are readily available to one of skill in the art. (c) A patent need not teach, and preferably omits, what is well known in the art (MPEP 2164.01). (d) The application at lines 8-29 on page 37 and at pages 64-71 does provide specific guidance as to preferred fragments of SEQ ID NO: 1331. (e) Working examples are not required to enable an invention. *In re Borkowald*, 422 F.2d 904, 906 (CCPA, 1970).

With regard to the quantity of experimentation required, Applicants contend that the quantity of experimentation is not undue because the synthesis of peptides is routine as is the screening of the peptides against 114-1 polyclonal antibodies to demonstrate whether the polypeptides are capable of eliciting an immune response against the '*Neisserial meningitidis* strain B'. Applicants cite *In re Wands*, 858, F.2d 731 (Fed. Cir. 1988) and state that the test is not merely quantitative, since the considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Applicants submit that similar to the monoclonal antibody in *In re Wands,* the 'experiment' of identifying polypeptides that fall within the scope of the claim involves design and synthesis of a family of peptides of a particular sequence and then screening for the ability to elicit an immune response against '*Neisserial meningitidis* strain B'. Applicants conclude that while the screening of polypeptides may take time much as screening for monoclonal antibodies, the screening is all routine, so the quantity of experimentation is not undue.

With regard to the relative skill of those in the art, Applicants contend that: (a) The skill in the art with respect to the presently claimed invention is quite high. (b) The presently claimed polypeptides are typically isolated by research scientists who are at least Ph.D. level with a fair

amount of post-doctoral experience or relevant industry experience. (c) Those of skill in the art are highly capable individuals with a high degree of familiarity with the screening methods needed to identify the claimed invention. (d) The claims are not unduly broad. Just as in *In re Wands*, the present application is directed to a polypeptide with a claimed function. (e) The monoclonal antibodies in *In re Wands* would actually have much greater sequence variation than the 70% identity as is presently claimed. (f) The presently claimed invention may be practiced by routine screening methods that will produce the claimed polypeptides. Given that the skill in the art is high just as *In re Wands*, and the breadth of the present claims is narrower than *In re Wands*, the amount of experimentation is not undue.

Applicants' arguments have been carefully considered, but are not persuasive. First, it is noted that Applicants have advanced no arguments with regard to the art-documented unpredictability established by the Office via the published teachings of McGuinness *et al.* (*Lancet* 337: 514-517, March 1991); Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, June 1976); McGuinness *et al.* (*Mol. Microbiol.* 7: 505-514, Feb. 1993); and Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986). The teachings from McGuinnes *et al.* were cited with specific reference to the unpredictability factor and the loss of specificity resulting from the substitution of a single amino acid not only within an epitope, but even outside an epitope of a *Neisseria meningitidis* polypeptide in particular. Applicants have simply dismissed these art-established facts. Secondly, the Office did not require Applicants to predict the exact sequence of every protein or polypeptide within the claim scope. Instead, the lack of enablement of even a single 30% non-identical polypeptide variant species (let alone a representative number of variant species to enable the variant genus now claimed) within the instant specification was brought to Applicants' attention in the face the art-documented teachings of McGuinness *et al.* (*Lancet* 337: 514-517, March 1991); Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, June 1976); McGuinness *et al.* (*Mol. Microbiol.* 7: 505-514, Feb. 1993); and Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986) on polypeptide variants. The only polypeptide that is enabled as claimed in the instant specification is the unaltered polypeptide of SEQ ID NO: 1331. This single non-variant polypeptide species is insufficient to enable the claimed

genus, which encompasses innumerable 1-30% structurally non-identical polypeptide variants concurrently having the recited function.

Applicants' analogy of the instantly claimed polypeptide variant having 30% sequence non-identity to SEQ ID NO: 1331 and Applicants' discussion of Federal Circuits' decision in *In re Wands* and the trial court's reversal, have been noted. Contrary to Applicants' assertion, the case involving the HBsAg monoclonal antibody is *not* similar to the presently claimed invention. As set forth previously, the instant claims are drawn to a purified polypeptide variant that is 100 amino acids or less in length and having 30% non-identity to SEQ ID NO: 1331 and concurrently comprising at least one antigenic determinant that elicits an immune response against 'Neisserial meningitidis strain B'. The instant claims are *not* drawn to a monoclonal antibody, or a 30% structurally varied, or 30% structurally non-identical monoclonal antibody having a specific binding function. Contrary to Applicants' assertion, a monoclonal antibody is *not* a peptide. Applicants are reminded that 'antibodies' are defined in the art as 'glycoprotein substances' (see Cruse *et al. Illustrated Dictionary of Immunology*, page 18, right column, 1997), and not as polypeptides. A 'glycoprotein' is defined in the art as a protein with one or more carbohydrate moieties attached thereto (see Glick DM. *Glossary of Biochemistry and Molecular Biology*, Revised Edition, Portland Press, London, page 75, 1997). Thus, a carbohydrate-containing 'antibody' is different from a 'polypeptide'. Unlike the instantly claimed polypeptide variants of the 18 amino acid-long SEQ ID NO: 1331, antibodies are much larger molecules. The conformation-dependent binding of a shorter polypeptide variant is not comparable to the binding functions of a much larger antibody glycoprotein. Therefore, Applicants' analogy of the claimed invention to HBsAg monoclonal antibody is misplaced.

Applicants are correct in that the instant specification discloses the one polypeptide sequence, SEQ ID NO: 1331. As clearly indicated in paragraph 18 of the final Office Action mailed 10/04/05, 'A purified polypeptide 100 amino acids or less in length wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 1331', and a composition comprising the same and a pharmaceutically acceptable carrier', are enabled and are free of prior art currently of record.

Contrary to Applicants' arguments, the existence of screening methods in the art does not automatically predict the immune response-eliciting function of a polypeptide variant that is 100 amino acids or less in length and that has as much as 30% sequence non-identity with the 18 amino

acid-long polypeptide of SEQ ID NO: 1331. Applicants are correct in that the quantity of experimentation is not undue for the routine synthesis of peptides and its screening with 114-1 polyclonal antibody. However, the screening of synthesized peptide variants against 114-1 polyclonal antibody does not establish whether the peptide variants are 'capable of eliciting an immune response against the '*Neisserial meningitidis* strain B'. Such screening with an antibody only establishes whether the synthesized peptide variants are antigenic. The art at the time showed that a substitution of one single amino acid within an epitope, or even outside an epitope changes the specificity of the peptide variant. See the teachings of McGuinness *et al.* below in paragraph 11. There is no disclosure within the instant specification that the claimed 30% identical polypeptide variant sequence containing an antigenic determinant which elicits an immune response against '*Neisserial meningitidis* strain B', has been deposited. Furthermore, the now recited '*Neisserial meningitidis* strain B' appears to be a specific strain that is required to practice the instant invention. Yet, it does not appear that the '*Neisserial meningitidis* strain B' is neither deposited by Applicants, nor is it publicly available. Without its public availability or deposition at a recognized depository, one of skill in the art would not be able to practice the instant invention without undue experimentation.

Production of a monoclonal antibody to a particular antigen of a known or unaltered structure requires a permissible amount of routine experimentation. In *In re Wands*, with regard to the making of a monoclonal antibody to a particular antigen, the structural composition of the antigen did not change by 30%, and therefore, making of a monoclonal antibody to an antigen of unaltered structure would require permissible amount of routine experimentation. The situation in the instant application is not the same. As set forth in paragraph 11 below, the art on microbial polypeptide antigens documents that a substitution of one or more amino acid residues within a reference polypeptide of known structure results in a polypeptide variant that is biologically or immunogenically different from the native or unmodified polypeptide. Houghten's teachings set forth below establish that although such a polypeptide variant may elicit a humoral antibody response, the resultant antibodies may not recognize the native polypeptide antigen, i.e., SEQ ID NO: 1331 in the instant case. A humoral or cellular immune response that does not recognize the native polypeptide cannot be expected to be immunospecific to the now recited '*Neisserial*

meningitidis strain B' and therefore, cannot be expected to be immunoprophylactic or therapeutic against an infection caused by '*Neisserial meningitidis* strain B'. The polynucleotide homologs or variants isolated solely based on percent identity or homology do not predictably display the functions of the native molecules, absent an independent showing that the variant polynucleotide sequence produces a polypeptide variant that functions as recited. The immunogenic functions of a gene product based solely on percent sequence identity is unreliable and unpredictable, absent a supportive showing by the production of a representative number of 1 to 30% non-identical polypeptide variant species that have the recited and required antigenic determinant which elicits an immune response against '*Neisserial meningitidis* strain B'. See paragraph 11 below for a detailed analysis.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

9) Claim 1 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, includes the limitations: wherein the polypeptide comprises at least one antigenic determinant that elicits an immune response against *Neisserial 'meningitidis* strain B' and has a length of 100 amino acids or less. However, there is no descriptive support in the specification for a purified polypeptide having at least 70% sequence identity to the amino acid sequence of SEQ ID NO: 1331 and concurrently having an antigenic determinant that has the ability to 'elicit an immune response against *Neisserial meningitidis* strain B'. The limitation of eliciting an immune response broadly encompasses elicitation of both humoral and cell mediated immune responses against *Neisserial meningitidis* strain B. The disclosure at lines 20-27 on page 3 of the specification however is limited to a reagent, including a protein reagent, 'which can raise antibodies', preferably against '*Neisseria meningitidis* strain B'. Therefore, the above-identified limitation in the claim(s) is considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are respectfully requested to point to the descriptive support in the specification

as filed, for the newly added limitation(s), or remove the new matter from the claim(s).

To overcome the rejection, it is suggested that Applicants replace the limitation 'that elicits an immune response' in claim 1 with the limitation --that can raise antibodies--.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Strain Deposit)

10) Claims 1, 10 and 25-32 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological material is (1) known and readily available to the public; (2) reproducible from the written description, e.g. sequenced; or (3) deposited.

Claim 1 as amended, recites what appears to be a specific bacterial strain: '*Neisserial meningitidis* strain B'. It is apparent that this '*Neisserial meningitidis* strain B' is required to practice the claimed invention. As a required element, this '*Neisserial meningitidis* strain B' must be known and be readily available to the public, or obtainable by a reproducible method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the '*Neisserial meningitidis* strain B'.

From a review of the instant specification, it appears that the '*Neisserial meningitidis* strain B' has not been deposited at a recognized depository in compliance with 37 C.F.R § 1.801-1.809. If the deposit has already been made under the provisions of the Budapest Treaty, filing of a signed affidavit or declaration by Applicants or assignees, or a statement by an attorney of record having a registration number who has authority and control over the conditions of deposit, is required stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that **all** restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each state. Further, the statement should identify the deposited '*Neisserial meningitidis* strain B' by its depository accession number, establish that the deposited '*Neisserial meningitidis* strain B' is the same as the one described in the specification, and that the deposited '*Neisserial meningitidis* strain B' was in Applicants' possession at the time of filing. As a means of satisfying the necessary criteria of the deposit rules and to show that the recited

'*Neisserial meningitidis* strain B' is the same as the one deposited, Applicants may submit a copy of the contract or a notice of acceptance of the '*Neisserial meningitidis* strain B' by the depository.

Applicants' attention is directed to *In re Lundack*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 C.F.R § 1.801-1.809 for further information concerning deposit practice.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

11) Claims 1, 10 and 25-32 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a purified polypeptide having a length of 100 amino acids or less comprising the amino acid sequence of SEQ ID NO: 1331, does not reasonably provide enablement for a polypeptide having a length of 100 amino acids or less (i.e., 5, 10, 20, 25, 35, 50, 70 amino acids etc. up to 100) and comprising a contiguous amino acid sequence with 'at least 70% sequence identity to SEQ ID NO: 1331', wherein the polypeptide comprises at least one antigenic determinant 'that elicits immune response against *Neisserial meningitidis* strain B', as claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Instant claims are evaluated based on *Wands* factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

Instant claims as amended, encompass a purified polypeptide comprising a contiguous amino acid sequence with at least 70% sequence identity to the 18 amino acid-long amino acid sequence of SEQ ID NO: 1331, wherein the purified polypeptide has a length of 100 or less, i.e., 5, 10, 20, 25, 40, 50 etc. up to 100, amino acids and comprises at least one antigenic determinant 'that elicits immune response against *Neisserial meningitidis* strain B'. First, there is no bacterium by name '*Neisserial meningitidis*' in the art. The recited '*Neisserial' meningitidis* strain B appears to be a specific strain of *Neisseria meningitidis* of unspecified serogroup, serotype, subtype, or

immunotype, as opposed to be a *Neisseria meningitidis* strain of serogroup B. The limitation 'immune response' encompasses both humoral or antibody-mediated and cellular or cell-mediated immune response. The limitation 'polypeptide .... comprising a contiguous amino acid sequence with at least 70% sequence identity to the sequence of SEQ ID NO: 1331' encompasses purified polypeptides comprising contiguous amino acid sequences with at least 30% non-identity to the sequence of SEQ ID NO: 1331. The specification indicates diagnostic applications as well as therapeutic and vaccination (prophylactic) intentions. See lines 17-19 and 28-30 of page 3; line 13 of page 4 of the specification; section 'Immunodiagnostic Assays' on pages 33 and 34 of the specification; and section 'Vaccines' on pages 23-25 o the specification. The 'antigenic determinant' is described as including a B-cell epitope and a T-cell epitope (see line 7 of page 5 of the specification). The claimed product is intended for use as an agent that treats, ameliorates or prevents a desired disease (see lines 20-25 of page 22 of the specification). In other words, the recited polypeptide variant that is 100 amino acids in length or less and having at least 30% non-identity with the amino acid sequence of SEQ ID NO: 1331 is *required* to have the antigenic determinant which elicits a humoral and/or cellular immune response against '*Neisserial meningitidis* strain B'. The diagnostic, therapeutic and prophylactic applications described in the specification indicate that the claimed composition comprising the at least 30% non-identical polypeptide variant is meant for use in diagnosis, treatment, or prevention of '*Neisserial meningitidis* strain B' infections. However, there is *not one single* showing within the instant specification that a polypeptide having a length of 100 amino acids or less when varied or altered to have at least 30% non-identity to SEQ ID NO: 1331 would retain the ability to elicit a humoral and/or cellular immune response against '*Neisserial meningitidis* strain B'. Not a single polypeptide variant species (let alone a representative number of variant species) having a length of 100 amino acids or less and having at least 30% non-identity to SEQ ID NO: 1331 is shown to 'elicit an immune response against the specifically recited strain of '*Neisserial meningitidis* strain B'. The full scope of the instant claims is not enabled. There is absolutely no showing of a correlation between the primary or tertiary structure of a polypeptide variant having a length of 100 amino acids or less and that is at least 30% structurally non-identical to SEQ ID NO: 1331 and its humoral and/or cellular immunogenic functions against '*Neisserial meningitidis* strain B'. There is no showing that these

polypeptide variants tolerate modifications and remain immunogenic with respect to '*Neisserial meningitidis* strain B'. With this lack of showing, the Office would look into the literature in the relevant art of polypeptide or peptide variants in order perform the required *Wands* analysis.

A review of the state of the art at the time of the invention, particularly with regard to unpredictability as associated with meningococcal proteins documents the following. The art shows that an alteration even in a single amino acid can eliminate or drastically change one or more biologic function(s) of the polypeptide. For instance, McGuinness *et al.* (*Lancet* 337: 514-517, March 1991, already of record) showed that a point mutation generating a single amino acid change in a P1.16-specific epitope in the VR2 region of the *porA* gene of a strain of *Neisseria meningitidis* of subtype P1.7,16 resulted in "striking changes in the structural and immunological properties of the class 1 protein" of this isolate (see abstract and page 514). With particular reference to VR1 and VR2 epitopes of class 1 outer membrane protein of *Neisseria meningitidis*, McGuinness *et al.* (*Mol. Microbiol.* 7: 505-514, Feb 1993, already of record) also taught that "[a] single amino acid change *within an epitope*, or an amino acid deletion *outside an epitope*, were both associated with *loss of subtype specificity* resulting from a change in the predicted conformation at the apex of the loop structure" (see abstract) [Emphasis added]. One of skill in the art can reasonably expect a loss of immunospecificity to '*Neisserial meningitidis* strain B' in Applicants' polypeptide variant which has as much as 30% non-identity to the amino acid sequence of SEQ ID NO: 1331. It should be noted that Applicants have neither identified a functional site, i.e., an antigenic determinant that elicits an immune response against *Neisseria meningitidis* strain B, in any single polypeptide variant that is 70%, 80%, or 90% identical to the amino acid sequence of SEQ ID NO: 1331, for one of skill in the art to avoid or to include mutation(s) or variation(s) within or outside the antigenic determinant. The lack of disclosure and specific guidance within the instant specification combined with the art-recognized functional unpredictability would require one of skill in the art to engage in considerable amount of undue experimentation.

With regard to the structure-function relationship of an amino acid sequence in general, Rudinger *et al.* (*In*: *Peptide Hormones*. (Ed) JA Parsons, University Park Press, June 1976, already of record) taught that 'the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study' (see page 6). Rudinger *et al.* further taught that 'it is impossible to

attach a unique significance to any residue in a sequence' and that a 'given amino acid will not by any means have the same significance in different peptide sequences (i.e., fragments), or even in different positions of the same sequence (see page 3). The lack of guidance within the instant specification in combination with Rudinger's teachings supports the Office's position regarding the unpredictability factor and the need to engage in considerable amount of undue experimentation.

The state of the art on microbial polypeptides in general indicates that a random replacement affecting the epitopic amino acid positions that are critical to the three-dimensional conformational structure and specific binding property of a protein, would result in a polypeptide that may be non-functional, or not optimally antigenic as a diagnostic reagent, or not optimally immunogenic as a vaccine candidate, because such positions tolerate no or little modifications. For instance, Houghten *et al.* (New Approaches to Immunization, *Vaccines86*, Cold Spring Harbor Laboratory, p. 21-25, 1986, already of record) teach the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten *et al.* state (see page 24):

> One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively **unrecognizable** by any of the antibodies in the polyclonal pool. [Emphasis added].

Thus, it has already been established in the art that variations in critical residues at specific positions of an amino acid sequence could result in a polypeptide variant, which may induce an antibody that may not recognize or bind to the native polypeptide of a microorganism. In other words, although a polypeptide having as much as 30% sequence non-identity to the native polypeptide is likely to be immunogenic, there is no predictability that such a variant would remain immunospecific to '*Neisserial meningitidis* strain B'.

The above-cited references reasonably demonstrate that even a single amino acid substitution/deletion will often dramatically affect the immunospecific biological activity or characteristics of a protein or polypeptide. Clearly, with as much as 30% sequence non-identity to the polypeptide of SEQ ID NO: 1331, the *Neisseria meningitidis* strain B-specific immunogenic function of the claimed polypeptide variant cannot be predicted, merely based on the sequence similarity or identity with SEQ ID NO: 1331, nor would it be expected to be nearly the same as that of the polypeptide of SEQ ID NO: 1331. Although a skilled artisan might envision making a

number of changes in the reference polypeptide sequence of SEQ ID NO: 1331 in accordance with Applicants' disclosure, it is highly uncertain or unpredictable that the polypeptide variant as claimed would retain 'at least one antigenic determinant that elicits an immune response against *Neisserial meningitidis* strain B' as recited. If one nucleotide base in the nucleotide sequence that encodes the polypeptide of SEQ ID NO: 1331 is deleted or inserted at a single position within the coding sequence, all the codons down stream of that insertion or deletion would be frame-shifted. If that frame-shift took place near the 5' end of the gene, it is likely that the polypeptide expressed will have little in common structurally or functionally with the native polypeptide of SEQ ID NO: 1331. The polynucleotide homologs or variants isolated solely based on percent identity or homology do not predictably display the functions of the native molecules, absent an independent showing that the variant polynucleotide sequence produces a polypeptide variant that functions as recited. The immunogenic functions of a gene product based solely on percent sequence identity is unreliable and unpredictable, absent a supportive showing by production of a representative number of 1 to 30% non-identical polypeptide variant species that have the recited and required antigenic determinant which elicits an immune response against '*Neisserial meningitidis* strain B'. For all the reasons delineated above, making and using of the instantly claimed polypeptide variant having the recited ability to elicit an immune response against '*Neisserial meningitidis* strain B' is well outside the realm of routine experimentation. Accordingly, undue experimentation would have been required by one of ordinary skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed, due to the lack of specific guidance, the lack of enabling disclosure, the art-demonstrated functional unpredictability as reflected in the state of the neisserial or microbial polypeptide art, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

The Courts have held that it is the specification, not the knowledge of one skilled in the art that must supply the 'novel' aspects of an invention in order to constitute adequate enablement. See *Genentech Inc. v. Novo Nordisk A/S Ltd., 42 USPQ2d 1001)*. Moreover, the specification must have been enabling at the time the invention was made (see *In re Wright, 27 USPQ2d 1510*). A claim must be enabled over its whole breadth. In this respect, if there are doubts, substantiated by verifiable facts, there is lack of sufficient enablement.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) Claims 1, 10 and 25-32 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague, indefinite and/or incorrect in the recitation '*Neisserial*' *meningitidis* (see last line), because it is unclear what is encompassed in this limitation. The art recognizes *Neisseria meningitidis* bacterium, but not '*Neisserial*' *meningitidis,* as recited. Furthermore, it is unclear whether 'strain B' is the designation given to *Neisseria meningitidis* of any serogroup, or is it serogroup B *Neisseria meningitidis.*

(b) Claims 10 and 25-32, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

Remarks

13) Claims 1, 10 and 25-32 stand rejected.

A purified polypeptide 100 amino acids or less in length wherein the polypeptide comprises the amino acid sequence of SEQ ID NO: 1331, and a composition comprising the same and a pharmaceutically acceptable carrier, are free of prior art currently of record.

14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number (571) 273-8300, which receives facsimile transmissions 24 hours a day and 7 days a week.

15) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

16) Any inquiry concerning this communication or earlier communication(s) from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail service. The Examiner can normally be reached on Monday to

Friday from 7.15 a.m to 4.15 p.m. except one day each bi-week which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

June, 2006

S. DEVI, PH.D.
PRIMARY EXAMINER